High haemoglobin A1c level is a possible risk factor for ventricular fibrillation in sudden cardiac arrest among non-diabetic individuals in the general population

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Aims	This study aimed to establish whether higher levels of glycated haemoglobin (HbA1c) are associated with increased sudden cardiac arrest (SCA) risk in non-diabetic individuals.
Methods and results	Case–control study in non-diabetic individuals (HbA1c < 6.5%) in the Netherlands. Cases were SCA patients with electrocardiogram (ECG)-documented ventricular fibrillation (VF, the predominant cause of SCA) and HbA1c measurements immediately after VF, prospectively included in September 2009–December 2012. Controls (up to 10 per case) were age/sex-matched non-SCA individuals, included in July 2006–November 2007. We studied 306 cases (56.4 ± 6.8 years, 79.1% male) and 1722 controls (54.0 ± 6.8 years, 64.8% male). HbA1c levels were higher in cases than in controls (5.8 ± 0.3% vs. 5.4 ± 0.3%, $P < 0.001$). The proportion of increased HbA1c (≥5.7%) was 63.1% in cases and 19.3% in controls ($P < 0.001$). Multivariate regression models indicated that increased HbA1c was associated with a > six-fold increased VF risk [adjusted odds ratio (OR_{adj}) 6.74 (5.00–9.09)] and that 0.1% increase in HbA1c level was associated with 1.4-fold increase in VF risk, independent of concomitant cardiovascular risk factors. Increased VF risk at higher HbA1c is associated with acute myocardial infarction (MI) as cause of VF [OR 1.14 (1.04–1.24)], but the association between HbA1c and VF was similar in non-MI patients [OR 1.32 (1.21–1.44)] and MI patients [OR 1.47 (1.37–1.58)].
Conclusion	Among non-diabetic individuals, risk of VF increased with rising HbA1c levels, independent of concomitant cardiovascular disease. Future studies should establish whether HbA1c level may be used as biomarker to recognize individuals at risk for VF.
Keywords	Sudden cardiac arrest • Haemoglobin A1c • Prevention • Ventricular fibrillation • Prediabetes

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What's new?

- Increased ventricular fibrillation (VF) risk exists not only in patients with diabetes but also in individuals with impaired blood glucose control (> six-fold increased VF risk).
- Even in individuals without cardiovascular disease risk factors increased HbA1c was associated with VF risk.

Introduction

Sudden cardiac arrest (SCA) remains a general health problem, causing 20% of deaths in industrialized societies.[1] The predominant cause of SCA is malignant ventricular arrhythmias (ventricular fibrillation, VF). Recognition of individuals at risk of VF is presently limited and predictors of VF must be discovered. Diabetes mellitus Type 2 (DM) is a known risk factor for VF. Increased VF risk in DM patients is mediated by multiple factors, in particular, higher incidence of cardiovascular disease (CVD), i.e. coronary artery disease and myocardial infarction (MI).[2,3] Other DM-related factors, e.g. autonomic neuropathy,[4,5] QT prolongation,[6] and hyperglycaemia may also increase VF risk.[2] In DM patients, reduction in blood levels of glycated haemoglobin A1c (HbA1c; this marker reflects average blood glucose levels in the preceding 2–3 months) is associated with lower risk of coronary artery disease, non-fatal MI, and SCA in numerous,[7–9] but not all[10] studies. Consistent with this finding, in non-diabetic individuals, increasing HbA1c levels are associated with increasing CVD risk.[11,12] However, whether higher HbA1c levels in non-diabetics are associated with VF is not established, as only few studies are available, and these studies show inconsistent results or have important methodological limitations.[2,13] An association between HbA1c and VF risk is plausible, since DM-related pathophysiologic changes, some of which increase VF risk, may already exist in non-diabetic individuals whose blood glucose control is impaired, but not sufficiently abnormal for the diagnosis of DM.

We hypothesized that individuals with impaired blood glucose control have increased VF risk. Studying these individuals has great significance since their numbers are on the rise in the present obesity epidemic. These individuals can be identified by increased HbA1c levels ($\geq$5.7% and <6.5%; HbA1c $\geq$6.5% is generally considered DM). Thus, testing our hypothesis may also provide an indication of whether HbA1c levels may be developed as biomarker for VF risk in these individuals. We conducted a case–control study to compare HbA1c levels between out-of-hospital SCA cases with ECG-documented VF and matched non-SCA controls. To investigate whether a possible association is influenced by manifest CVD or CVD risk factors, we separately assessed the relation between HbA1c levels and VF risk in individuals with CVD or CVD risk factors and in those without. Moreover, as previous studies in DM-patients have shown an association between HbA1c and both non-fatal MI[8,11] and MI,[12] we investigated whether higher HbA1c levels in non-diabetic individuals are associated with a larger proportion of MI as cause of VF, and whether higher VF risk at increased HbA1c levels exists both in the presence and absence of MI.

Methods

Study design

In this case–control study, we compared patients with out-of-hospital SCA with ECG-documented VF (cases) to age/sex-matched non-SCA individuals (controls). Cases were consecutively included from the ARREST registry[14] in the period September 2009–December 2012. Controls were selected from the New Hoorn Study in the period July 2006–November 2007.[15] The Institutional Review Boards approved the ARREST registry and New Hoorn Study, and all SCA survivors and study participants, respectively, provided written informed consent. Our investigation complies with the Declaration of Helsinki.

Inclusion of study participants and data collection

Cases

Details of the ARREST registry were published previously.[14] In short, all out-of-hospital SCA resuscitation attempts occurring in a contiguous study region (North-Holland province of the Netherlands, urban and rural areas, population 2.4 million) were registered in collaboration with all emergency medical services and hospitals in the study region. Of all registered SCAs, resuscitation ECGs were collected to ascertain presence of VF; SCA cases without ECG-documented VF were excluded from the present study because it could not be ruled out that SCA resulted from non-cardiac causes (e.g. stroke, ruptured aneurysm, pulmonary embolism) in these patients. Medical information was retrieved from the treating hospital or the general practitioner (GP) to establish the presence of CVD risk factors. The immediate cause of VF (MI vs. no MI) was retrieved from hospital records. Medication use in the year before SCA was retrieved from the patients' pharmacists. HbA1c was prospectively obtained from blood samples collected upon hospital arrival of all VF cases who were transported to the Academic Medical Center Amsterdam during the study period. HbA1c measurements were performed at the clinical chemistry laboratory of this hospital by cation exchange chromatography using HPLC technology (Tosoh G8 Automated Glycohemoglobin Analyzer, Goffin Meyvis, Etten-Leur, The Netherlands).

For the present study, we included VF cases aged 40–65 years (the age range of the control cohort) in whom a cardiac cause of SCA was verified from hospital records ($n = 799$). Patients were excluded when consent could not be retrieved ($n = 70$), they died before hospital admission ($n = 119$), no blood was drawn ($n = 114$), HbA1c measurement was missing or failed ($n = 36$), or their medical history could not be retrieved ($n = 42$). Cases with known DM as diagnosed by a GP and cases who used anti-diabetes medication ($n = 59$) or in whom HbA1c levels were above the cut off level of 6.5% ($n = 53$) were also excluded. The final study case sample consisted of 306 cases.

Controls

Controls were participants of the New Hoorn Study, a population-based study on DM, in which information is recorded on manifest CVD and CVD risk factors along with plasma HbA1c levels of 2807 men or women aged 40–65 years from the general population of the town of Hoorn, the Netherlands.[15] The New Hoorn study was selected as non-SCA control cohort because its study region is located entirely within the area covered by ARREST. All HbA1c measurements were performed at the clinical chemistry laboratory of the VU University Medical Center Amsterdam, using Diabetes Control and Complications Trial standardized reverse-phase cation exchange chromatography (HA 8160 analyser; Menarini, Florence, Italy) in blood taken under fasting and standardized

conditions.[15] For the present study, we excluded participants with HbA1c levels ≥6.5% or those who used glucose-lowering treatment (*n* = 27), with known DM (*n* = 85), missing HbA1c (*n* = 20), or missing medical history (*n* = 296). Up to 10 controls were matched to each case based on age (±1 year) and sex. After exclusion of 657 controls who could not be matched to a case, the final matched control sample used for this study consisted of 1722 controls.

Definitions

We considered manifest CVD and CVD risk factors as potentially confounding to the association between HbA1c level and VF. Cardiovascular disease (yes/no) was defined as previous MI or previous stroke. Cardiovascular disease risk factors (yes/no) were defined as current smoking, hypertension, hypercholesterolaemia, or obesity. Cardiovascular disease and smoking status were physician-reported in cases and self-reported in controls, both by questionnaire. In both cases and controls, hypertension was defined as physician-reported and/or use of antihypertensive drugs; hypercholesterolaemia as physician-reported, use of antilipidaemic drugs, or total plasma cholesterol level ≥6.5 mmol/L; obesity as physician-reported or body mass index >30 kg/m². Additionally, increased HbA1c was defined as an HbA1c of 5.7–6.4%, according to the guidelines of the American Diabetes Association.[16]

Statistical analysis

Continuous variables are presented as mean ± standard deviation, and categorical data are absolute numbers and proportions. Normal distribution of the data was tested using Shapiro–Wilk's test and data were normally distributed. Differences between cases and controls were tested using the χ^2 test or Student's *t* test, where appropriate.

The association between 0.1% point increase in HbA1c levels and VF risk was estimated using conditional logistic regression analysis. The assumption of linearity was checked by making quartiles for the cases and applying the same cut-offs to the controls; this confirmed that the assumption of linearity was valid. Additionally, the analysis was performed with increased HbA1c (yes/no) as predictor of VF. To address the possibility of confounding by concomitant CVD or CVD risk factors, we performed multivariate conditional logistic regression analyses, adjusting for CVD and CVD risk factors (Model 1), or CVD propensity score (Model 2). Cardiovascular disease propensity score was the predicted probability of having suffered VF based on CVD or CVD risk factors. Additionally, a sensitivity analysis was performed using propensity score matching for the probability of being a case with age, sex and the confounders of Model 1. A calliper of 0.1 was used, with matching of 1 to a maximum of 10 controls.

The presence of interaction on a multiplicative scale between HbA1c and CVD, CVD risk factors, and sex was estimated by consecutively including the cross-product of the two factors as a variable in Model 1. To further investigate a possible confounding effect by the presence of CVD or CVD risk factors, we studied the relation between HbA1c levels (using the categorical variable) and VF risk stratified according to presence of CVD or CVD risk factors. In these unmatched subgroups, multivariate logistic regression analysis with adjustment for age, sex, and presence of CVD or CVD risk factors, where appropriate, was performed to estimate the association with VF. Among cases with a known hospital-diagnosed cause of VF, HbA1c levels were compared between cases whose immediate cause of VF was MI, and those with other causes using Model 1. Additionally, among cases with a known hospital-diagnosis and their matched controls, the association between HbA1c levels and VF was stratified by cause (MI vs. non-MI).

We considered a *P*-value <0.05 as statistically significant. All statistical analyses were performed using the SPSS software package for Mac (SPSS for Mac, version 20.0, SPSS Inc.).

Results

We identified 306 eligible cases (mean age 56.4 years, 79.1% male) and 1722 matched controls (54.0 years, 64.8% male, *Figure 1*). Mean HbA1c level was higher in cases than in controls [39.5 ± 3.4 vs. 35.6 ± 3.4 mmol/mol (5.8 ± 0.3 vs. 5.4 ± 0.3%), *P* < 0.001], and increased HbA1c was present in 63.1% of cases compared to 19.3% of controls (*P* < 0.001, *Table 1*). The distribution of HbA1c levels was shifted towards higher values in cases compared to controls (*Figure 2*). Previous MI, previous stroke, smoking, hypertension, and/or hypercholesterolaemia were more prevalent among cases than controls, but obesity was not (*Table 1*).

Every 0.1% point increase in HbA1c was associated with a 1.4-fold increase in VF risk in the whole cohort, as we observed in both models (*Table 2*); additionally, increased HbA1c (5.7–6.4%) was associated with a > six-fold increased VF risk {odds ratio (OR$_{model1}$) 6.7 [95% confidence interval (CI): 5.0–9.1]; OR$_{model2}$ 6.1 (95% CI: 4.6–8.3)}.

Figure 3 shows the stratified analysis for the association between HbA1c and VF risk according to sex, presence of CVD, and presence of CVD risk factors. The association appeared to be stronger in female patients, but the interaction between sex and Hba1c was not statistically significant (*P* = 0.130). Similarly, no significant interaction between presence of CVD and the association between HbA1c and VF risk was observed (*P* = 0.829). However, presence of CVD risk factors showed a significant interaction with the association between HbA1c and VF risk (*P* = 0.033); in patients without CVD risk factors this association was stronger [OR 9.58 (5.54–16.57)] than in those with CVD risk factors [OR 5.68 (4.11–7.85)].

Propensity score matching resulted in a selection of 89.2% of cases and 89.9% of controls, excluding the outliers (Supplementary material online, *Table S1*). Our sensitivity analyses using propensity score matching showed similar results as our multivariate analyses with an OR of 1.39 (1.32–1.46) for every 0.1% point increase of HbA1c and 5.93 (4.41–7.98) for increased HbA1c (Supplementary material online, *Table S2*).

To analyse whether increased VF risk at elevated HbA1c levels is associated with a larger proportion of MI as cause of VF, we studied 279 cases with known MI status (MI, *n* = 187; non-MI, *n* = 92), excluding 27 cases whose MI status was unknown because they died before a diagnosis was made. Mean HbA1c was higher in cases in whom VF was caused by MI than in cases in whom it was not (5.8 ± 0.3 and 5.7 ± 0.3%, respectively; *P* = 0.013). We found a significant association between HbA1c and MI status [OR 1.14 (1.04–1.24), *P* = 0.005] with adjustment for age, sex, CVD, and CVD risk (Supplementary material online, *Table S3*). In our stratified analysis in patients with known hospital-diagnosis and their matched controls (cases *n* = 279, controls *n* = 1596), the association between HbA1c and VF was similar in the MI and non-MI groups [OR 1.47 (1.37–1.58) and 1.32 (1.21–1.44), respectively].
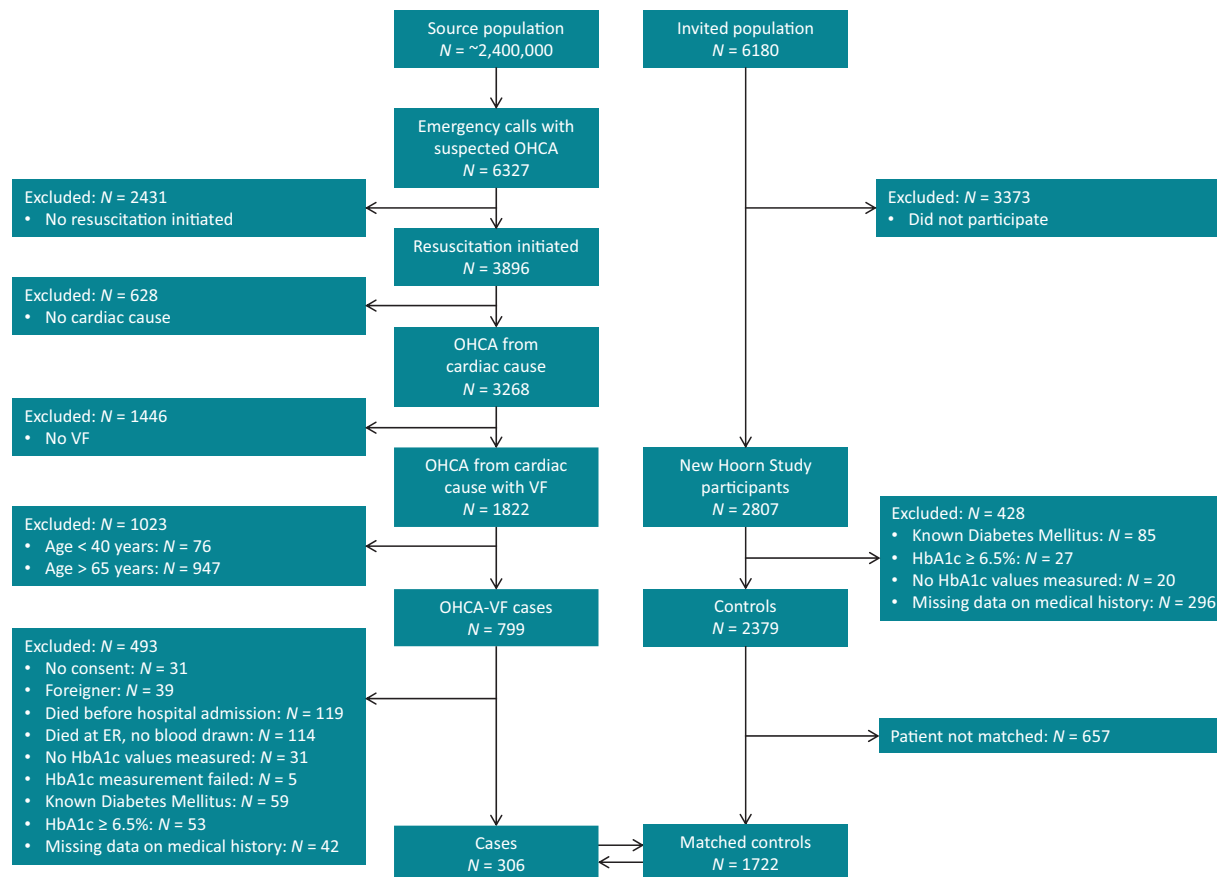
Figure 1 A flowchart of patient inclusion. ER, emergency room; HbA1c, glycated haemoglobin; OHCA, out-of-hospital cardiac arrest; VF, ventricular fibrillation.

Table 1 **Baseline characteristics of the study population**

	Cases (n = 306)	Controls (n = 1722)	P-value[a]
Mean HbA1c (mmol/mol), mean ± SD	39.5 ± 3.4	35.6 ± 3.4	<0.001
Percentage point, mean ± SD	5.8 ± 0.3	5.4 ± 0.3	<0.001
ADA-criteria			
Normal HbA1c (<5.7%)	113 (36.9)	1390 (80.7)	<0.001
Increased HbA1c (≥5.7%)	193 (63.1)	332 (19.3)	
Age (years), mean ± SD	56.4 ± 6.8	54.0 ± 6.8	<0.001
Male sex	242 (79.1)	1116 (64.8)	<0.001
Cardiovascular disease			
Previous MI	47 (15.4)	48 (2.8)	<0.001
Previous stroke	17 (5.6)	0 (0.0)	<0.001
Cardiovascular disease risk factors			
Smoking	137 (44.8)	364 (21.1)	<0.001
Hypertension	120 (39.2)	455 (26.4)	<0.001
Hypercholesterolaemia	101 (33.0)	429 (24.9)	0.003
Obesity	46 (15.0)	242 (14.1)	0.651

Data are expressed as n (%) unless indicated otherwise.
ADA, American Diabetes Association; HbA1c, glycated haemoglobin; MI, myocardial infarction; SD, standard deviation.
[a]Continuous variables were tested with Student's t-test or ANOVA. Binary variables were tested with the χ^2 test.

Discussion

We found an association between HbA1c levels and VF risk among individuals without known or newly diagnosed DM. Individuals with increased HbA1c had > six-fold increased VF risk compared to individuals with normal HbA1c (<5.7%) after adjustment for established risk factors for VF (smoking, hypertension, hypercholesterolaemia, and obesity). The association between HbA1c and VF risk was also found among individuals without any concomitant CVD risk factors, and it was similarly strong in patients whose VF was caused by MI as in patients in whom VF was not caused by MI. Still, this association was modified by MI as cause of VF, as compared to other causes.

SCA in adults predominantly occurs in an out-of-hospital setting and is often the first sign of heart disease.[17] Given that survival rates after out-of-hospital SCA are low, prevention is crucial. Yet, our ability to recognize individuals at risk is poor, and discovery of risk markers is needed. In accordance with the observation that DM is a major risk factor for SCA, glucose intolerance was also found to increase SCA risk.[9] That study found, in a subgroup analysis in non-diabetes patients, an OR (95% CI) of 1.31 (1.06–1.61), while we found 1.41 (1.33–1.48). This difference may be explained by the fact that that study had no ECG confirmed SCA. Additionally, the HbA1c levels measured in the cases included in our study were measured very close to the arrhythmic event, while the blood samples from the study of Patel *et al.*[9] used blood samples not specifically close to the arrhythmic event (but at an unspecified time during follow-up of the cohorts). Nevertheless, future studies should establish whether HbA1c level is a useful biomarker to recognize increased VF risk among non-diabetic individuals with or without CVD.

The increased SCA risk in DM patients has usually been explained by the observation that HbA1c values predict the development of
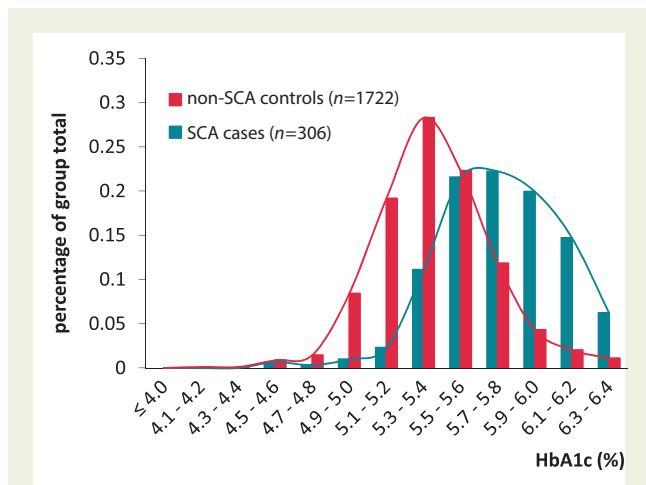

Figure 2 Distribution of HbA1c levels among SCA cases and non-SCA controls without diabetes mellitus. HbA1c, glycated haemoglobin; SCA, sudden cardiac arrest.

Table 2   Odds ratios of the association between HbA1c and sudden cardiac arrest in individuals without diabetes

	OR$_{crude}$	95% CI	Model 1 OR$_{adjusted}$	95% CI	Model 2 OR$_{adjusted}$	95% CI
HbA1c[a]	1.44	1.37–1.51	1.42	1.35–1.50	1.41	1.33–1.48
Increased HbA1c[b] (≥5.7%)	7.44	5.58–9.93	6.74	5.00–9.09	6.14	4.55–8.30

Model 1: OR adjusted for presence of cardiovascular disease (previous myocardial infarction and previous stroke) or cardiovascular risk factors (hypertension, hypercholesterolaemia, smoking, and obesity). Model 2: OR adjusted for propensity score.
CI, confidence interval; HbA1c, glycated haemoglobin; OR, odds ratio.
[a]ORs calculated with HbA1c levels defined as a continuous variable, OR expressed per 0.1% increase in HbA1c.
[b]ORs calculated with HbA1c levels defined as a binary variable according to American Diabetes Association guidelines.[16]
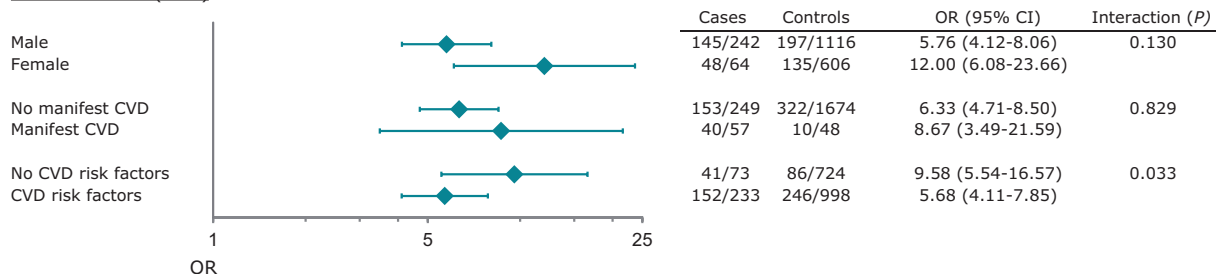

Figure 3 Stratified analyses of risk of ventricular fibrillation in relation to increased HbA1c. Matched analysis for sex adjusted for presence of CVD and CVD risk factors. Unmatched analysis for manifest CVD and CVD risk factors adjusted for age, sex, and presence CVD or CVD risk factors, where appropriate. CI, confidence interval; CVD, cardiovascular disease; HbA1c, glycated haemoglobin; OR, odds ratio.

CVD.[11] This hypothesis is supported by our finding of higher HbA1c levels among patients with MI as the cause of VF. However, in our study, MI was not the cause of VF in a substantial number of cases, and the association between HbA1c levels and VF risk was similarly strong in MI and non-MI patients. Moreover, our study and others report that SCA risk increased with rising HbA1c levels even among individuals without CVD,[2,9] suggesting that other mechanisms may play an additional role. We can only speculate about the nature of these mechanisms. First, in non-diabetic individuals, impaired fasting glucose levels (leading to increased blood glucose levels and high-normal HbA1c levels) and hyperinsulinaemia are associated with QTc interval prolongation and higher heart rates.[6] Prolonged QTc intervals are independently associated with SCA in the general population,[18] whereas higher heart rates in these individuals may suggest increased sympathetic activity (a risk factor for cardiac arrhythmia and SCA[19]) and the presence of autonomic neuropathy. Second, changes which predispose to malignant cardiac arrhythmias (e.g. myocardial fibrosis) may have already developed at high-normal HbA1c levels (5.7%).[20]

The major strengths of our study are its prospective design and the rigorous ascertainment of a cardiac cause of SCA, based on the requirement of ECG-documentation of VF. Previous studies defined SCA by death certificates. Yet, death certificate-based ascertainment of SCA significantly overestimates the incidence of SCA.[21] Moreover, unlike other studies which correlated single baseline HbA1c or glucose measurements to events occurring many years later,[22] including malignant ventricular arrhythmias,[13] we measured HbA1c in blood samples drawn immediately after arrival at the hospital. HbA1c reflects average blood glucose levels of the past 2–3 months preceding measurement and is a relatively stable measure which is not much affected by daily fluctuations of blood glucose or fasting/non-fasting state. Therefore, our rationale was that changes in blood glucose levels following VF are not (or only marginally) reflected in HbA1c levels measured immediately after VF and that it is unlikely that these HbA1c levels had significantly changed between time of VF and time of measurement.

Limitations

Our study has some limitations. First, the HbA1c assays and circumstances of the blood sampling used for cases and controls were different. While these disparities may account for some variation, it is unlikely that they fully explain the large differences in HbA1c levels that we observed between cases and controls. Although HbA1c measurements were done in two different laboratories, these laboratories had similar precision and accuracy, as we learned from inspection of their reports for the Foundation of Quality Control for Medical Laboratories. Second, not all data on confounders could be obtained in a similar manner for cases and controls. However, the presence of risk factors in the control group was based on medication use and measurements, prescribed and performed by a physician, and done in a similar way as for cases. Therefore, we believe that these data can be compared with our case data. Moreover, we did not use a nested case–control design; however, by using propensity score matching on the probability to be a case, we tried to balance the case and control populations. Additionally, although we performed an age/sex-matched case–control study in which we

aimed to match one case to up to 10 controls, we obtained more matches for younger and female cases, resulting in a younger control cohort with a more female sex distribution. To address this issue, we performed conditional logistic regression analysis and a propensity score-matched analysis. Moreover, we assumed that HbA1c levels reflect blood glucose control both in DM patients and in individuals from the community without DM. Lastly, residual confounding may remain from factors unavailable for analysis.

Conclusion

Increasing HbA1c values in non-diabetic individuals are associated with increased VF risk. This association is also present in non-diabetic individuals without CVD or in patients in whom VF was not caused by MI, suggesting that non-CVD mechanisms are present. Future studies are suggested to research whether HbA1c levels are useful as biomarker for VF risk in non-diabetic individuals. If so, HbA1c may be included in risk scores to recognize individuals at risk and used as simple screening tool for VF risk in (primary) clinical practice.

Supplementary material

Supplementary material is available at *Europace* online.

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